4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-1721]

Agency Information Collection Activities; Proposed Collection; Comment Request; Investigational New Drug Application Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing an opportunity for public comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of 1995 (PRA), Federal Agencies are required to publish notice in the *Federal Register* concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on information collection associated with investigational new drug application requirements.

DATES: Submit either electronic or written comments on the collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2014-N-1721 for "Agency Information Collection Activities; Proposed Collection; Comment Request; Investigational New Drug Applications." Received comments, those filed in a timely manner

(see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501-3521), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the *Federal Register* concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Investigational New Drug Applications--21 CFR part 312

OMB Control Number 0910-0014--Revision

This information collection supports implementation of provisions of section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and of the licensing provisions of the Public Health Service Act (42 U.S.C. 201 *et seq*.) that govern investigational

new drugs and investigational new drug applications (INDs). Implementing regulations are found in part 312 (21 CFR part 312), and provide for the issuance of guidance documents (see § 312.145 (21 CFR 312.145)) to assist persons in complying with the applicable requirements. The information collection applies to all clinical investigations subject to section 505 of the FD&C Act and include the following types of INDs:

- An Investigator IND is submitted by a physician who both initiates and investigates, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with § 312.23 or § 312.20 (21 CFR 312.23 or 312.20). It is also used for patients who do not meet the criteria of an existing study protocol or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and FDA's review takes place.

There are two IND categories: commercial and research (non-commercial)

General IND requirements include submitting an initial application as well as amendments to that application; submitting reports on significant revisions of clinical investigation plans; submitting information to the clinical trials data bank (https://clinicaltrials.gov) established by the National Institutes of Health/National Library of Medicine, including expanded information on certain clinical trials and information on the results of these clinical trials; and reporting information on a drug's safety or effectiveness. In addition, sponsors are required to provide to FDA an annual summary of the previous year's clinical experience. The regulations also include recordkeeping requirements regarding the

disposition of drugs, records regarding individual case histories, and certain other documentation verifying clinical investigators' fulfillment of responsibilities.

Form FDA 1571 entitled "Investigational New Drug Application (IND)" and Form FDA 1572 entitled "Statement of Investigator," were developed to assist respondents with the information collection and provide for uniform reporting of required data elements. The information is required to be submitted electronically. Individuals who are interested in receiving printed forms may send an email request to the FDA Forms Manager at formsmanager@OC.FDA.GOV. Fees may apply. Sponsors (including sponsor-investigators) interested in filing or updating a research IND may use a new web-based interface developed for use by mobile device or desktop to help in completing Form FDA 1571. The web-based interface also allows respondents to electronically submit completed Form FDA 1571 and associated files. For more information regarding Forms FDA 1571 and 1572 visit https://www.fda.gov/news-events/expanded-access/how-complete-form-fda-1571-and-form-fda-1572.

Human drug, biological product, and device product submissions must be accompanied by Form FDA 3674, "Certification To Accompany Drug, Biological Product, and Device Applications or Submissions." The guidance document "Form FDA 3674 – Certifications To Accompany Drug, Biological Product, and Device Application" (November 2017) is available from our website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/form-fda-3674-certifications-accompany-drug-biological-product-and-device-applicationssubmissions and provides instruction on completing and submitting this information to FDA. As communicated in the instructions, the certification must accompany the application or submission and be included at the time of submission to FDA.

Regulations in part 312, subpart B, specify content and format requirements for applications, amendments, annual reporting, and withdrawals, including content and format

requirements for protocol and information amendments. The regulations also explain phases of an investigation and set forth principles of IND submissions.

Regulations in part 312, subpart C, describe administrative actions pertaining to respondents' requests for and responses to clinical holds, terminations, and inactive IND status determinations, as well as various types of meetings (for example, End-of-Phase 2 and Pre-new drug application (NDA) meetings).

Regulations in part 312, subpart D, set forth sponsor and investigator responsibilities, including general responsibilities; transfer of obligations to a contract research organization; recordkeeping and record retention controls; reporting responsibilities; and responsibility for disposition of unused supply of investigational drug. The regulations also provide for investigator controls including review of ongoing investigations; compliance with requirements regarding the protection of human subjects and institutional review board assurance; and disqualification of clinical investigators.

Regulations in part 312, subpart E, sets forth requirements applicable to drugs intended to treat life-threatening and severely debilitating illnesses. The regulations establish procedures to reflect that physicians and patients accept greater risk or side effects from products that treat life-threatening and severely debilitating illnesses than they would accept from products that treat less serious illnesses. The procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.

Regulations in part 312, subpart F, include provisions pertaining to import and export requirements; foreign clinical studies not conducted under an IND; the disclosure of data and information in an IND; and the issuance of guidance documents. We are revising the information collection to account for burden that may be associated with recommendations found in Agency guidance documents.

- The guidance document entitled "Oversight of Clinical Investigations" (August 2013) communicates risk-based monitoring strategies and recommends plans for investigational

studies of medical products, including human drug and biological products, medical devices, and combinations thereof. The guidance document is intended to enhance human subject protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting. The guidance also communicates that sponsors can use a variety of approaches to fulfill responsibilities for monitoring clinical investigator conduct and performance in IND studies, and provides a description of strategies for monitoring activities to reflect a modern, risk-based approach.

- The guidance document entitled "Pharmacogenomic Data Submissions" (March 2005) provides recommendations intended to assist sponsors submitting or holding INDs, NDAs, or biologics license applications (BLAs) with submission requirements for relevant data regarding drug safety and effectiveness (including §§ 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2, and 601.12 (21 CFR 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2 and 601.12)). Because the regulations were developed before the advent of widespread animal or human genetic or gene expression testing, the regulations do not specifically address when such data must be submitted. The guidance document includes content and format recommendations regarding pharmacogenomic data submissions. Although we have not received any pharmacogenomic submissions since 2013, we assume an average of 50 hours for preparing and providing information to FDA as recommended in the guidance and estimate one submission annually.
- The guidance document entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics" (December 2019) was developed to assist sponsors and applicants submitting INDs, NDAs, BLAs, or supplemental applications on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biologic. The guidance document describes important principles for designing, conducting, and reporting the results from an adaptive clinical trial, and advises sponsors

on the types of information to submit to facilitate FDA evaluation of clinical trials with adaptive designs, including Bayesian adaptive and complex trials that rely on computer simulations for their design.

The referenced guidance documents are available for download from our website at https://www.fda.gov/regulatory-information/search-fda-guidance-document and were issued consistent with § 312.145 to help respondents comply with requirements in part 312. In publishing the respective notices of availability for each guidance document, we included an analysis under the PRA and invited public comment on the associated information collection recommendations. In addition, all Agency guidance documents are issued in accordance with our Good Guidance Practice regulations in 21 CFR 10.115, which provide for public comment at any time.

Regulations in part 312, subpart G, provide for drugs for investigational use in laboratory research animals or in vitro tests.

We estimate the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden for Biologics[1]

21 CFR Section; Information Collection Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Subpart A--General Provisions: §§ 312.1 through 312.10					
§ 312.2(e); requests for FDA advice on the applicability of part 312 to a planned clinical investigation	454	1.528	694	24	16,656
§ 312.8; requests to charge for an investigational drug	14	1.64	23	48	1,104
§ 312.10; waiver requests	5	1	5	24	120
Subtotal Subpart A Center for Biologics Evaluation and Research (CBER)			722		17,880
Subpart B--Investigational New Drug Application (IND): §§ 312.20 through 312.38 (Including Forms FDA 1571, 1572, and 3674)					
§ 312.23(a) through (f); IND content and format	2,075	3.382	7,018	300	2,105,400
§ 312.30(a) through (e); Protocol amendments	1,781	4.6692	8,316	284	2,361,744
§ 312.31(b); information amendments	169	2.48	419	100	41,900
§ 312.32(c) and (d); IND Safety reports	224	10.59	2,372	32	75,904
§ 312.33(a) through (f); IND Annual reports	971	2.2739	2,208	360	794,880
§ 312.38(b) and (c); notifications of withdrawal of an IND	712	3.057	2,177	28	60,956
Subtotal Subpart B CBER			22,510		5,440,784
Subpart C--Administrative Actions: §§ 312.40 through 312.48					

§ 312.42; clinical holds and requests for modification	154	1.65	254	284	72,136
§ 312.44(c) and (d); sponsor responses to FDA when IND is terminated	86	1.22	105	16	1,680
§ 312.45(a) and (b); sponsor requests for or responses to an inactive status determination of an IND by FDA	48	1.48	71	12	852
§ 312.47; meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings	157	1.80	283	160	45,280
Subtotal Subpart C CBER			713		119,948
Subpart D--Responsibilities of Sponsors and Investigators: §§ 312.50 through 312.70					
§ 312.53(c); investigator reports submitted to the sponsor, including Form FDA - 1572, curriculum vitae, clinical protocol, and financial disclosure	1,068	5.23	5,586	80	446,880
§ 312.54(a); sponsor submissions to FDA concerning investigations involving an exception from informed consent under § 50.24	4	4.25	17	48	816
§ 312.54(b); sponsor notifications to FDA and others concerning an institutional review board determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in § 50.24(a)	1	1	1	48	48
§ 312.55(a); number of investigator brochures submitted by the sponsor to each investigator	473	2.224	1,052	48	50,496
§ 312.55(b); number of sponsor reports to investigators on new observations, especially adverse reactions and safe use	243	4.95	1,203	48	57,744
§ 312.56(b), (c), and (d); review of ongoing investigations and associated notifications; sponsor notifications	915	2.948	2,698	80	215,840
§ 312.58; inspection of records and reports by FDA	7	1	7	8	56
§ 312.64; number of investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports	2,728	3.816	10,411	24	249,864
§ 312.70; disqualification of a clinical investigator by FDA	5	1	5	40	200
Subtotal Subpart D CBER			20,980		1,021,944
Subpart F--Miscellaneous: §§ 312.110 through 312.145					
§ 312.110(b)(4) and (b)(5); number of written certifications and written statements submitted to FDA relating to the export of an investigational drug	18	1	18	75	1,350
§ 312.120(b); number of submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND	280	9.82	2,750	32	88,000
§ 312.120(c); number of waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND	7	2.29	16	24	384
§ 312.130; number of requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24	350	1.342	470	8	3,760

Subtotal Subpart F CBER			3,254		93,494
Total			48,179		6,694,050

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Recordkeeping Burden for Biologics[1]

21 CFR Section; Information Collection Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
Subpart D--Responsibilities of Sponsors and Investigators: §§ 312.50 through 312.70					
§ 312.52(a); sponsor records for the transfer of obligations to a contract research organization	94	2.26	212	2	424
§ 312.57; sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug, and any financial interest	335	2.70	904	100	90,400
§ 312.62(a); investigator recordkeeping of the disposition of drugs	453	1	453	40	18,120
§ 312.62(b); investigator recordkeeping of case histories of individuals	453	1	453	40	18,120
Subtotal Subpart D CBER			2,022		127,064
Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests					
§ 312.160(a)(3); records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests	111	1.40	155	0.5 (30 minutes)	78
§ 312.160(c) shipper records of alternative disposition of unused drugs	111	1.40	155	0.5 (30 minutes)	78
Subtotal Subpart G CBER			310		156
Total			2,332		127,220

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3.--Estimated Annual Reporting Burden for Human Drugs[1]

21 CFR Section; Information Collection Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Subpart A--General Provisions					
§ 312.2(e); requests for FDA advice on the applicability of part 312 to a planned clinical investigation	419	1	419	24	10,056
§ 312.8; requests to charge for an investigational drug	25	1.28	32	48	1,536
§ 312.10; requests to waive a requirement in part 312	68	1.5	102	24	2,448
Subtotal Subpart A Center for Drug Evaluation and Research (CDER)			553		14,040
Subpart B--Investigational New Drug Application (IND)					
§ 312.23(a) through (f); IND content and format (including Forms FDA 1571 and 3674)	4,886	1.4662	7,164	300	2,149,200
§ 312.30(a) through (e); protocol amendments	11,847	3.2367	38,346	284.25	10,899,850
§ 312.31(b); Information amendments	8,094	3.30899	26,783	100	2,678,300
§ 312.32(c) and (d); IND safety reports	892	15.848	14,137	32	452,384
§ 312.33(a) through (f); IND annual reports	3,777	2.9097	10,990	360	3,956,400
§ 312.38(b) and (c); notifications of withdrawal of an IND	1,549	1.834	2,841	28	79,548
Subtotal Subpart B CDER			100,261		20,215,682
Subpart C--Administrative Actions: §§ 312.40 through 312.48					

§ 312.42; clinical holds and requests for modifications	181	1.28	232	284	65,888
§ 312.44(c) and (d); sponsor responses to FDA when IND is terminated	1	1	1	16	16
§ 312.45(a) and (b); sponsor requests for or responses to an inactive status determination of an IND by FDA	213	1.72	367	12	4,404
§ 312.47; meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings	174	2.885	502	160	80,320
Subtotal Subpart C CDER			1,102		150,628
Subpart D--Responsibilities of Sponsors and Investigators					
§ 312.54(a); sponsor submissions to FDA concerning investigations involving an exception from informed consent under § 50.24	7	1.14	8	48	384
§ 312.54(b); sponsor notifications to FDA and others concerning an institutional review board determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in § 50.24(a)	2	1	2	48	96
§ 312.56; review of ongoing investigations and associated notifications	4,570	5.4689	24,993	80	1,999,440
§ 312.58; inspection of records and reports by FDA	73	1	73	8	584
§ 312.70; disqualification of a clinical investigator by FDA.	5	1	5	40	200
Subtotal Subpart D CDER			25,081		2,000,704
Subpart F--Miscellaneous: §§ 312.110 through 312.145					
§ 312.110(b)(4) and (b)(5); written certifications and written statements submitted to FDA relating to the export of an investigational drug	8	22.375	179	75	13,425
§ 312.120(b); submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND	1,964	7.352	14,440	32	462,080
§ 312.120(c); waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND	68	1.5	102	24	2,448
§ 312.130; requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24	3	1	3	8	24
§ 312.145; Guidance Documents:					
Oversight of Clinical Investigations (2013)	88	1.5	132	4	528
Pharmacogenomic Data Submissions (2005)	1	1	1	50	50
Adaptive Designs for Clinical Trials of Drugs and Biologics (2019)	55	4.727	260	50	13,000
Subtotal Subpart F CDER			15,117		491,555
Total			142,114		22,872,609

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 4.--Estimated Annual Recordkeeping Burden for Human Drugs[1]

21 CFR Section; Information Collection Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
Subpart D--Responsibilities of Sponsors and Investigators					
§ 312.52(a); transfer of obligations to a contract research organization	466	3.107	1,448	300	434,400

Table 4.--Estimated Annual Recordkeeping Burden for Human Drugs[1]

21 CFR Section; Information Collection Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
§ 312.57; records showing the receipt, shipment, or other disposition of the investigational drug and any financial interests	13,000	1	13,000	100	1,300,000
§ 312.62(a); records on disposition of drugs	13,000	1	13,000	40	520,000
§ 312.62(b); records on case histories of individuals	2,192	6.587	14,439	40	577,560
Subtotal Subpart D CDER			41,887		2,831,960
Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests					
§ 312.160(a)(3); records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests	547	1.43	782	0.50 (30 minutes)	391
§ 312.160(c); shipper records of alternative disposition of unused drugs	547	1.43	782	0.50 (30 minutes)	391
Subtotal			1,564		782
Total			43,451		2,832,742

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

The information collection reflects program changes and adjustments. We have revised the information collection to account for burden that may be incurred by respondents who choose to adopt or implement recommendations discussed in referenced Agency guidance documents intended to assist respondents in complying with regulatory requirements in part 312. We have also made adjustments to individual collection elements. As a result of these changes and adjustments, the information collection reflects an overall decrease in both annual responses and burden hours. Finally, we have removed burden we attribute to provisions in part 312, subpart I: Expanded Access to Investigational Drugs for Treatment Use and are revising OMB control number 0910-0814 to include burden associated with information collection applicable to these regulatory provisions for efficiency of Agency operations.

Dated: November 17, 2021.

Lauren K. Roth,

Associate Commissioner for Policy.

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